

Easy Pathology

— Dr. Abdelrahman Khalifa —

Chapter 5

Granuloma

Part 1



VISIT...

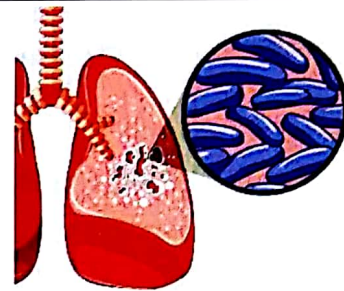
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Granuloma

Chronic non specific inflammation, forming mass of Epithelioid cells, surrounded by lymphocytes

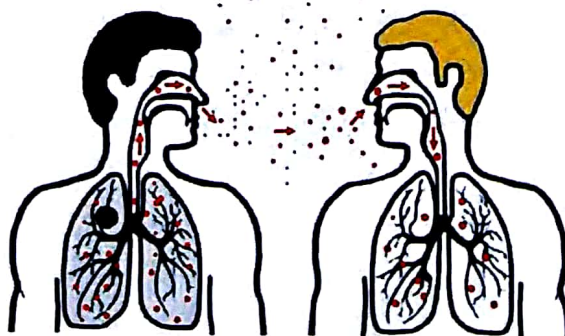
- **Infective**
 - **Bacterial:** **TB**, Cat scratch disease
 - **Parasitic:** **Bilharziasis**, Filariasis, Toxoplasma
 - **Fungal:** **Mycetoma**, Blastomycosis, Cryptococcus
- **Foreign body** granuloma : Silica, Suture, and Silicon granuloma in breast
- **Idiopathic** : **Sarcoidosis**, Crohns disease

Tuberculosis



Aetiology

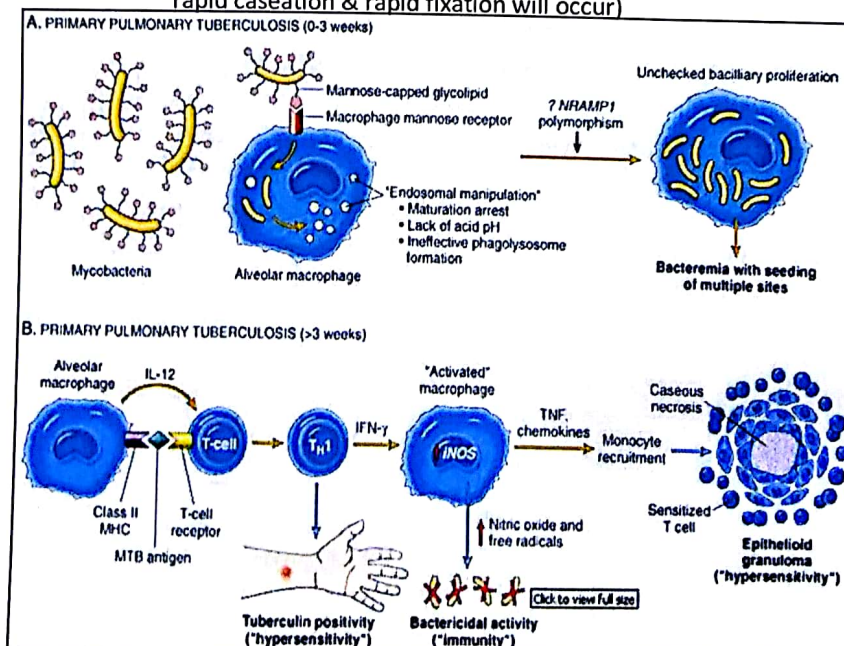
- **Organism:** **Mycobacterium TB** (*Human type* - *Bovine type*)
 - **Structure:** Cylindrical , contain Antigenic Protein, Carbohydrate, and Lipid Capsule (Resist heat , dryness, Lysosomes, F.R., Acid fast, alcohol fast)
 - **Virulence:** *Non motile, non toxin producing, killed by U.V.*
 - **Stain** (*stained with Ziehl-Neelsen*)
- **P.F. :**
 - **Low immunity** (*AIDS, D.M., Malnutrition, Alcoholism, Silicosis*)
 - **Crowding** (inhalation)
 - **Genetic** (Afro-American) : mutated NRAMP1 (natural resistance associated macrophage protein 1) → decreased killing ability of macrophage
- **Mode of transmission**
 - **Inhalation** : *droplets – dust* → *Tonsils - Lung*
 - **Ingestion** : *raw milk, or infected sputum* → *tonsils - intestine*
 - **Inoculation:** *Infected meat – Infected materials* → *infect Skin wounds (rare)*
 - **Intrauterine:** *transplacental* → *congenital TB*



Pathogenesis & Host response to T.B.

• Proliferative reaction (cellular reaction)

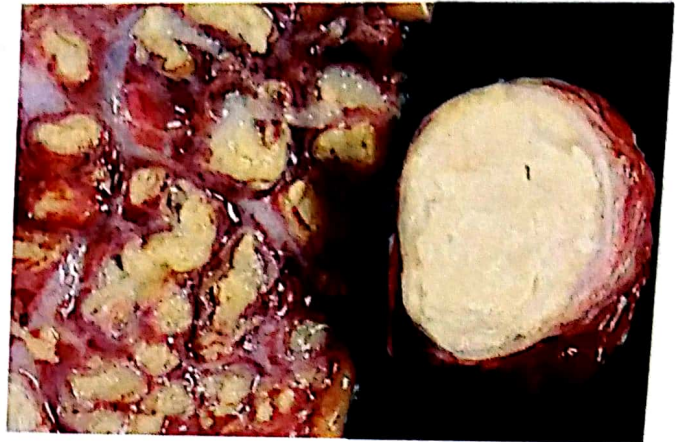
- **Neutrophils** are attracted → **destroyed** by organisms
- **Lipid** part of bacteria → attract **Macrophage** → phagocytosis of bacteria → replicate inside macrophage → without lysosomal damage
- **Macrophage** → secrete **IL-12** & present Ag to **T Lymphocytes** after **3 weeks**
Th0 → became **T helper1 CD4**
- **Th1 CD4** → (hypersensitivity type IV) → secrete several Lymphokines:
 - **IL2** → proliferation of lymphocytes
 - **IFN-gamma** → **Activation of macrophage** (strong killers & contain NO free radical)
 - **Activated macrophage** → secrete **TNF** → aggregation & transformation into → **Epithelioid cells**
 - Activated macrophage → **PDGF, TGF-B** → enhance fibrosis
 - Epithelioid cells: large, with abundant cytoplasm, vesicular nucleus, indistinct membrane
 - Epithelioid cells became → Giant cells:
 - **Langhan's giant cell**: Multineucleated, horse-shoe arrangement
 - **Foreign body giant cell**: clustered nuclei in the center or one pole
 - **MIF** → Fixation of epithelioid cells & giant cells
 - Activation of **CD8** → **Caseation** cytotoxic factor → Kill macrophage → Tissue caseation
 - **Inflammatory mediators** → +ve skin test
 - **Transfer factor** → immune system sensitization (In case of 2ry T.B. → rapid caseation & rapid fixation will occur)



- **Exudative reaction (excess fluid exudate)**

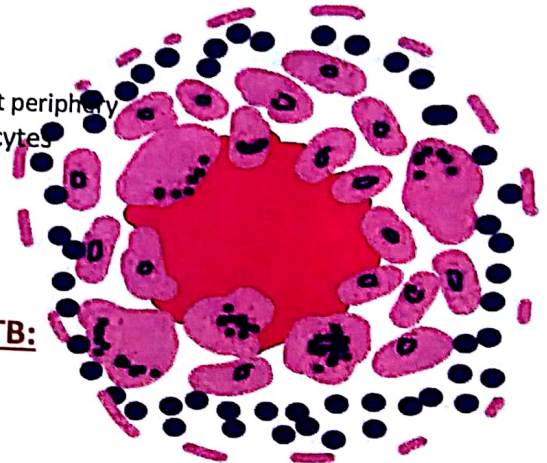
- Occur in Serous sacs
- In More Sensitive individuals (excess T lymphocytes)
- More Severe infection due to less immunity

Gross: tubercles, grey then → yellowish white (caseation) , Firm → soft cheesy



Microscopic: Tubercle (granuloma)

- **Early:**
 - Epithelioid cells (describe?)
 - Giant cells (describe?)
 - Lymphocytes (peripheral)
- **Late**
 - Caseation: homogenous pink, contain bacteria at periphery
 - remnants of cells : Epithelioid, giant, lymphocytes
 - Fibroblasts surrounding granuloma



Fate and complication of TB:

- Fibrosis
- Capsulation → Reactivation
- Calcification
- Cold abscess (extensive liquefaction of caseation) in **Bone, joints, LN, testis**
 - It accumulates or open by a tract of granulation tissue (sinus)
- **Severe Caseation** → bleeding, & blood spread
- **Secondary Amyloidosis** (discussed later)
- **Spread:**
 - **Local** : by **macrophage** (bacteria is non-motile)
 - **Lymphatic** (**More In 1ry TB**) → TB Lymphangitis & TB Lymphadenitis.
 - **Blood** (**More in 2ry TB**)
 - Caseation → penetrate blood vessels arteries or veins
 - Arterial invasion → spread in same organ
 - Venous invasion → spread into different organs
 - Spread could be:
 - Limited spread (*in single organ*) → isolated organ TB
 - Disseminated (*less immunity*) → Miliary TB in multiple organs
 - **Natural passages :**
 - **Bronchi**, from tonsils or larynx
 - **Bladder**, from kidney
 - **Peritoneum** from TB salpingitis
 - **Pleural spread**

	1ry TB	2ry TB
Infection	1 st time infection No sensitization	2 nd time infection (Reactivation – Reinfection) Sensitization present → exaggerated response
Age	More in Children	More in Adults
Sites	Tonsils – Lung – Intestine - Skin	Previous organs or Any site
Caseation	Less	More extensive
Pathological lesion	1ry complex: TB focus Lymphangitis Lymphadenitis (e.g. Tabes mesenterica)	L.N. & lymph vessels are less affected
Blood spread	Less	More

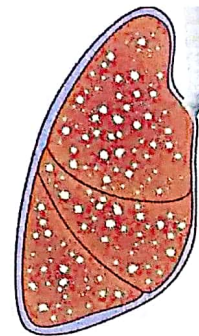
Miliary T.B. Multiple tuberculous foci due to blood spread in the same organ or distant organs

Causes: blood spread

Gross: multiple foci – small 2mm – grayish white

micro: granuloma (no fibrosis- no caseation)

Fate: Systemic miliary TB in multiple organs → fatal



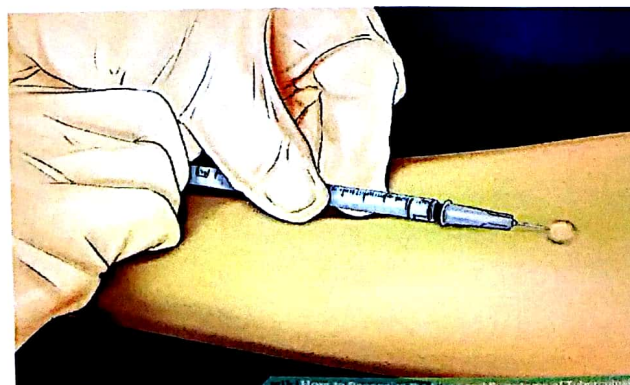
N.B.

Immunization

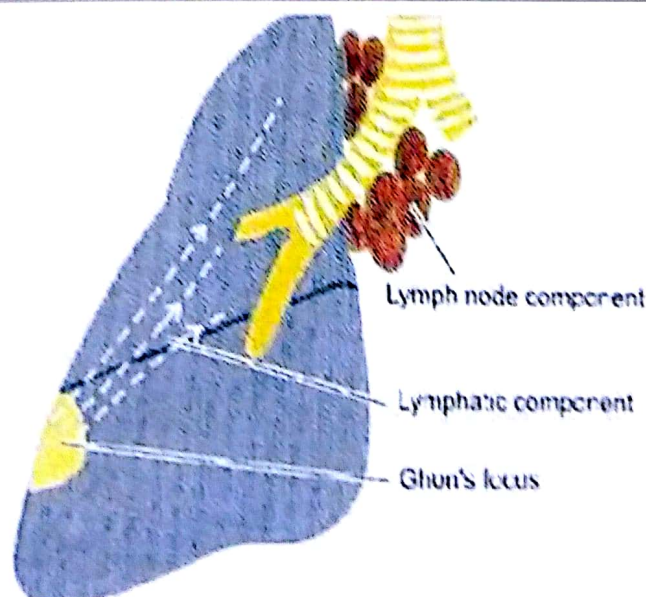
BCG (Attenuated bovine bacteria), given by injection → induction of hypersensitivity (cell-mediated) → Skin lesion is healed by fibrosis

Tuberculin test

Injection of 0.1 ml of (PPD) → Skin induration 0.5 cm within 2 days → patient is infected or immunized

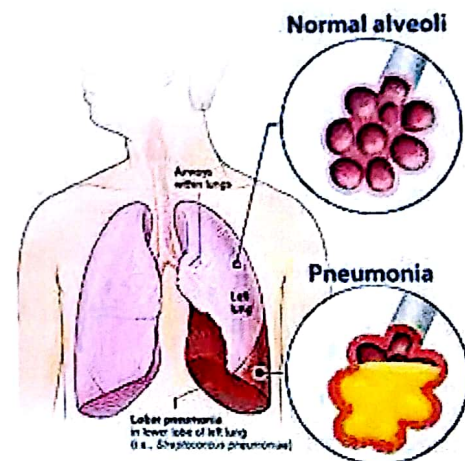
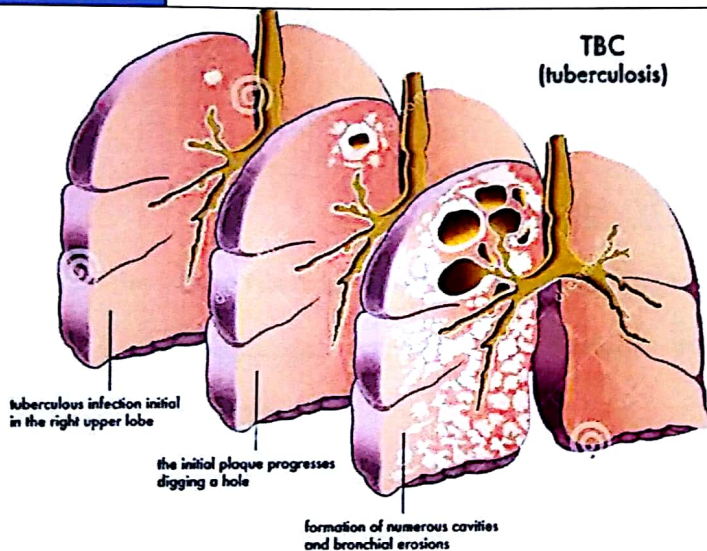


	1ry pulmonary TB Childhood TB	2ry pulmonary TB Adulthood TB
Infection	1 st time infection (inhalation)	Re infection In sensitized patient Reactivation (In AIDS, Cancers, Cortisone)
Age	More in Children	More in Adults
Sites	-Right lung -Between upper & lower lobes -Peripheral (sub-pleural)	Re infection : Apex (less blood, more air, more lymphatics) Re activation : previous site of Gohns focus
Morphology	1ry pulmonary complex: 1- Ghon's focus 1-2 cm (yellowish white- soft cheesy – rounded) micro: ...describe.... 2- Lymphangitis (Chain of tubercles) 3- Lymphadenitis (hilar LN)	- Assman's focus Apical TB focus 1-2 cm (describe..)→ cavitation & fibrosis <u>Pathogenesis:</u> Preexisting sensitization → Less L.N. enlargement , but more caseation
Fate	- <u>Fibrosis & calcification</u> - Capsulation & reactivation - <u>In Low immunity</u> : Progressive TB: Acute TB pneumonia Spread: Lymphatic & blood (military)	- Regression by fibrosis (good immunity) - Progression (low immunity): 1- Progressive Chronic fibro-caseous TB 2- Acute TB pneumonia

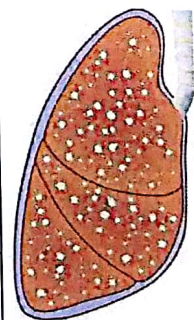


Progressive pulmonary TB

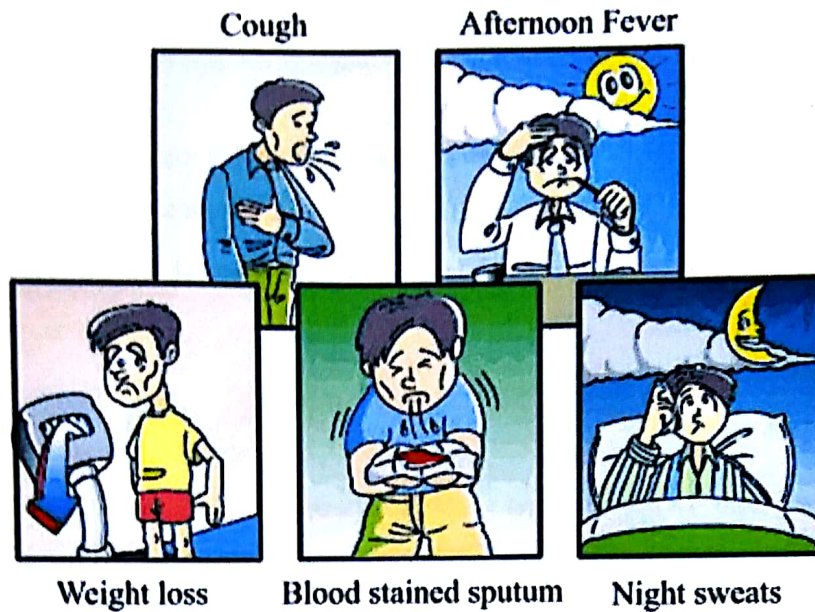
	Chronic fibro-caseous TB	Acute TB pneumonia
Course	Chronic, slowly progressive	Rapidly fatal TB
Immunity	Better Immunity Less Hypersensitivity	Immunity is very low (e.g. AIDS) more Hypersensitivity
Morphology	- Apical Cavity is irregular surrounded by fibrous capsule. Cavity is traversed by perforated bronchi & blood vessels. - Multiple small basal foci - L.N.: Minimal enlargement	- Consolidation in middle and lower lobe - No cavitation - L.N.: Enlargement (rapid spread)



Chronic fibro-cas. TB	Miliary TB
Spread through bronchi or lymphatics	Spread through blood vessel
less numerous	More numerous lesions
Larger & variable in size	Small foci (1-2 mm)
Yellowish (caseation)	Grayish white (no caseation)
Minimal L.N. enlargement	No L.N. enlargement



Clinical picture of Pulmonary TB



complications of pulmonary TB

- Lung Fibrosis & calcification → right sided H.F.
- Cavitations : perforate → hemoptysis ruptured → pneumothorax , TB Empyema
- Spread:
 - Local → bronchitis, pleurisy , pericarditis
 - Lymphatic → T.B. Lymphadenitis → bronchial compression & dyspnea
 - Blood → Miliary TB
 - Sputum → 2ry TB of tongue, tonsils, larynx & 2ry intestinal TB
- Secondary Amyloidosis → Nephrotic syndrome

Sites of Primery complex

- 1ry cervical complex : TB focus in tonsils + Lymphangitis + Cervical Lymphadenitis
- 1ry pulmonary complex: Ghon's focus + Lymphangitis + Hilar Lymphadenitis
- 1ry intestinal complex: TB focus in small intestine + Lymphangitis + mesentric Lymphadenitis (tabes mesentric)

Schistosomiasis

Aetiology:

- **Organism:**
 - Schistosoma hematobium (*urinary, genital*)
 - Schistosoma Mansoni (*intestinal, hepatic*)
- **Mode of transmission :** *penetration of skin under water*

Pathogenesis:

1- Cercaria:

- Allergic Rash (penetration of skin → *type I* hypersensitivity) red macules, or papules

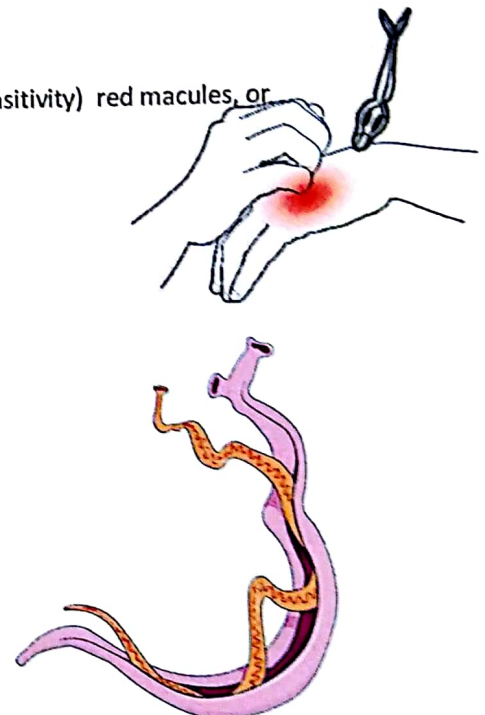
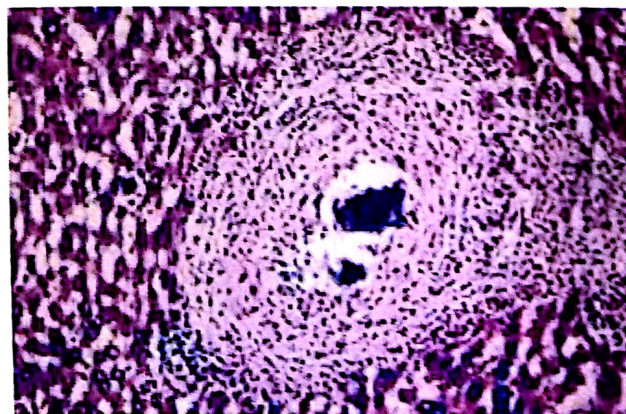
2- Worm

- Living worm
 - Not antigenic (covered by self protein)
 - Hemozoin pigment is taken by RES
- Dead worm
 - Embolism of veins by dead worm
 - Necrotizing-phelebitis
 - Angiomatoides (small arterio-venous shunts)

3- Ova:

- Granuloma :
 - Cellular granuloma: macrophage – Epithelioid cells – giant cells – **eosinophils**
 - surrounded with fibroblasts
 - healing with fibrosis

(Ova contain meracidium. Ova could be living, dead or **calcified**)



Urinary bilharziasis

Site: Trigone and posterior wall (ureteric orifices) – submucosa is the common site (?)

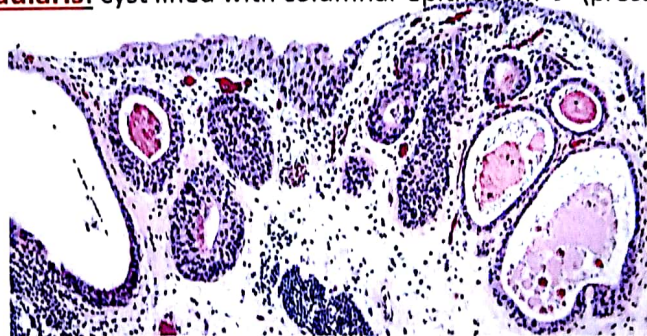
Gross:

- **Grain-like nodules** (yellow – surrounded by congestion)
- **Sandy patches** (granular grey patches – calcified ova in the wall + mucosal **atrophy**)
- **Polyps** Gross: Shape: sessile, or pedunculated or mulberry - Size: 2mm-2cm - red
Micro: Core: granulation tissue + granuloma (describe) - Covering: hyperplasia
- **Ulcers** : small – irregular
caused by: sandy patches or penetration by ova or polyp ulceration
- **Mucosal vesicles** (cystitis cystic)
- **Fibrosis of the wall or orifices**



Microscopic:

- **Bilharzial granuloma + bilharzial ova**
- **Epithelial (Urothelial) changes:**
 - **Hyperplasia & brunn's nest:** mass of transitional epithelium caused by dipping in submucosa (no invasion)
 - **Squamous metaplasia:** transform into str. Squamous → (precancerous)
 - **Leukoplakia:** excess keratinization of str. Squamous → (precancerous)
 - **Dysplasia & CIS:** cytological changes similar to cancer → (precancerous)
 - **Cystitis cystica:** cyst lined with transitional epithelium
 - **Cystitis glandularis:** cyst lined with columnar epithelium → (precancerous)



Complications:

- ☒ Bleeding → terminal hematuria → anemia
- ☒ 2ry infection of ulcers → PH changes → stones
- ☒ Fibrosis & contracted bladder :
 - closed bilharziasis → spread → pulmonary bilharziasis
 - Urinary tract obstruction → Urinary diverticulae - Hydronephrosis → **renal failure**
- ☒ Perforation → fistula
- ☒ Precancerous lesions (enumerate?) → **Carcinoma**

Intestinal bilharziasis

Aetiology: *Schistosoma mansoni* > *hematobium*

Site: Large Intestine (Rectum) – submucosa is the common site (?)

Morphology:

- **Early :** swollen red mucosa with petichae
- **Late:** sandy patches – polyps- ulcers – fibrosis

Complications:

- ☒ Bleeding → anemia
- ☒ 2ry Infection of ulcers → dysentery
- ☒ Fibrosis → closed bilharziasis → spread → hepatic bilharziasis
- ☒ Perforation → fistula - peritonitis
- ☒ Polyps → Intussusceptions & Intestinal obstruction



N.B : No precancerous epithelial lesions in Intestinal bilharziasis

Hepatic bilharziasis

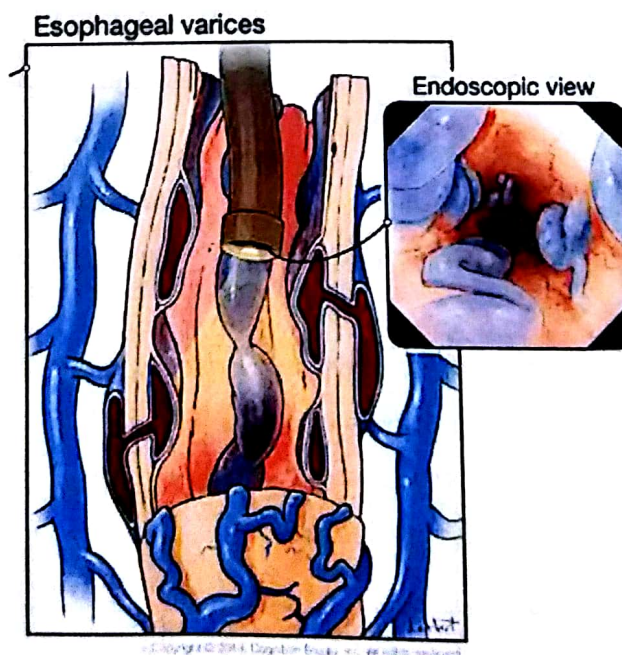
Pathogenesis: Following old intestinal bilharziasis (*Schistosoma mansoni*) → Intestinal fibrosis → **ova** accumulate in mesenteric veins → portal vein → deposits in **portal tracts** → granuloma & hepatic **periportal fibrosis**

Dead worm → emboli , thrombo-phlebitis & angiomatoid formation → portal hypertension

Gross	Size: early large → late : reduced Surface: Irregular retracted (<i>not cirrhotic</i>) C/S: thick white PT (<i>pipe stem</i>) Cons: firm 
Microscopic	-Portal tracts: - ova & Granuloma (<i>describe ...</i>) - Lesions by dead worm (<i>enumerate</i>) - Bile duct proliferation -Parenchyma: - Kupffer cell contain bilharzial pigment - Pigment in kupffer cells

Complications of Hepatic bilharziasis:

- **Portal hypertension & portal vein thrombosis**
 - **causes:** Portal tract fibrosis + Angiomatoides + parasitic emboli
 - **Effects:**
 - Congestive Splenomegaly
 - Ascitis (due to portal hypertension & hypoalbuminemia)
 - Dilated porto-systemic veins
 - *eosophageal varices* (submucosal blue bands) → *hematemesis*
 - *caput medausa*
 - *Piles* → *bleeding P/R*
 - Other complications of porto-systemic shunts:
 - *Ammonia encephalopathy*: toxic ammonia pass from intestine to brain through porto-systemic veins. And aggravated by disturbed liver function
 - *Pulmonary bilharziasis*: ova pass from intestine to systemic veins
- **Minimal disturbance of liver function**



Splenic bilharziasis

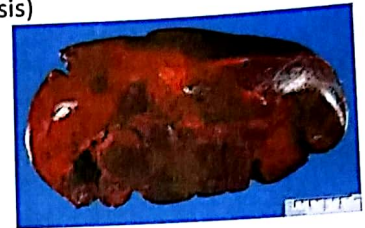
Circulating Ag → hyperplasia of lymphoid tissue
 Hepatic bilharziasis → portal hypertension → congestion of spleen

Gross: Large, brown, Thick capsule with cartilaginous metaplasia

Microscopic:

- Red pulp & sinusoids: dilated congested → ruptured → hemorrhage → forming **gandy-gamna** nodules (hemosedrin + Fibrosis)
- White pulp: Atrophic lymphoid follicles
- Littoral cell contain hemosedrin
- Capsule & trabeculae : thick

Complications: Compression & Hypersplenism



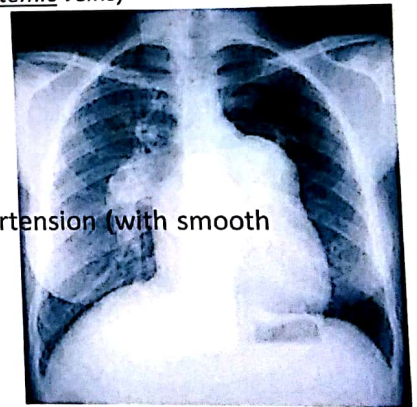
Pulmonary bilharziasis

Aetiology:

- Schistosoma hematobium (spread from urinary through systemic veins or vertebral)
- Schistosoma Mansoni (spread from intestinal → through porto-systemic veins)

Pathological changes

- Cercaria: irritation & cough
- Ova: granulomas (describe..) → fibrosis → pulmonary hypertension (with smooth muscle proliferation in arterioles)
- Dead worm:
 - Necrotizing arteriolitis
 - Verminous pneumonia : inflammatory cells - consolidation & severe necrosis



Complications:

- Lung fibrosis → pulmonary hypertension (Ayerza's disease):
 - Pulmonary atherosclerosis & thrombosis
 - Pulmonary aneurism
 - Right sided heart failure
- Verminous pneumonia → fatal

Hydatid disease

Aetiology:

- **Organism:** *Echinococcus granulosus*
- **P.F.:** Contact with infected animals (dogs, sheep, cattle)
- **Mode of transmission:** ingestion (contaminated food)

Sites: Liver (65%) - Lung - muscle - brain

Gross:

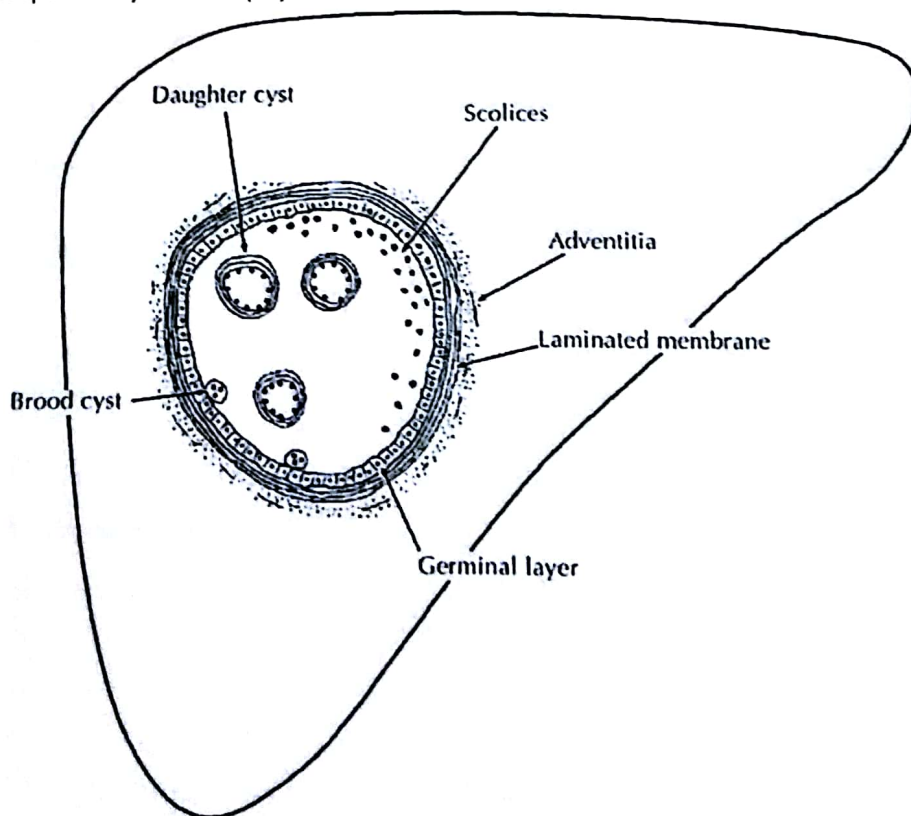
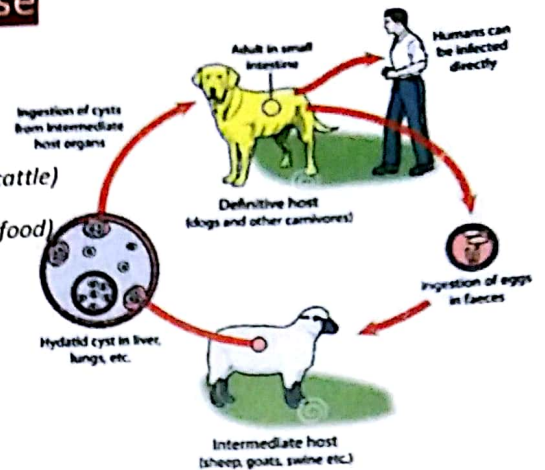
- **Shape:** rounded or oval cyst
- **Size:** 1 – 20 cm
- **C/S:** fluid – daughter cysts – white sand (calcified scolices)

Microscopic:

- Capsule (outer laminated – inner nucleated)
- Scolex & daughter cysts
- Surrounded by chronic inflammatory cells, excess eosinophils
- Fibrosis & Calcification

complications:

- Compression (e.g. obstructive jaundice – chest pain – bone fracture)
- Ruptured cyst → anaphylactic shock



Give reason:

- Extensive tissue caseation in 2ry TB
- Less L.N. enlargement in 2ry TB
- Minimal caseation in miliary TB
- Caseation in TB granuloma
- Portal hypertension in hepatic bilharziasis
- Urinary bilharziasis may predispose to cancer bladder
- Renal failure in case of old urinary bilharziasis

Complete:

- 1-Skin reaction to Cercaria is mediated byhypersensitivity, while granulomatous reaction is mediated byhypersensitivity.
- 2-Tuberclin test is positive in and
- 3-Multiple small uniform of TB foci are seen in T.B.
- 4-The commonest cause of death in complicated hepatic bilharziasis is.....
- 5-.....is a dipping mass of transitional epithelium
- 6-Cystitis glandularis may predispose to while Squamous dysplasia is predisposing to
- 7-Fibro-sidrotic nodules in splenic bilharziasis are named.....
- 8-1ry pulmonary complex is composed of,, &
- 9-Causes of bilharzial ulcers include.....,, &.....
- 10-Gohn's focus is found in.....of the lung, while Assman's focus is found inof the lung.

Caompare:

1ry – 2ry TB

Chronic fibrocaseous – Miliary TB

Gohn's focus – Assman's focus